Rejection Under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 1, 5, 7-10, 12-18, and 20-26 under 35 U.S.C. § 103(a) as unpatentable over Liao, et al., (U.S. Patent No. 6,147,109) in view of Niewohner, et al., (WO 99/24433); claims 6 and 19 under 35 U.S.C. § 103(a) as unpatentable over Liao, et al., (U.S. Patent No. 6,147,109) in view of Niewohner, et al., (WO 99/24433) and in further view of Doherty, et al., (U.S. Patent No. 6,037,346); claims 1, 5, 7-10, 12-18, and 20-26 under 35 U.S.C. § 103(a) as unpatentable over Liao, et al., (U.S. Patent No. 6,147,109) in view of R&D Drug Review (1998); and claims 6 and 19 under 35 U.S.C. § 103(a) as unpatentable over Liao, et al., (U.S. Patent No. 6,147,109) in view of R&D Drug Review (1998) and in further view of Doherty, et al., (U.S. Patent No. 6,037,346) (Paper No. 01242005, pages 2- 10). Applicants respectfully traverse.

The Examiner cites Liao, et al., (U.S. Patent No. 6,147,109) as the primary prior art over the claimed invention. Liao, et al., discloses the use of HMG-CoA reductase inhibitors to treat a myriad of conditions including, for example, pulmonary hypertension, stroke, heart failure, hypoxia-induced conditions, insulin deficiency, impotence, renal disease, gastric motility syndrome, atherosclerosis, transplant arterial sclerosis, arthritis, lupus, scleroderma, emphysema, etc. (*see, e.g.,* column 7, lines 34-52). In addition, Liao, et al., discloses an extensive list of "second agents" (>100 agents) that may be co-administered (column 13, line 14 to column 14, line 17). However, these second agents are very broad classes of pharmaceutical agents such as antagonist, cardiovascular agent, hormone, etc., and each individual class of agents represents a large number of compounds.

The Examiner states that "there is clear motivation for combining the components flows from their individually known common utility for treating erectile dysfunction" (Paper No. 01242005, page 4). The Examiner also states that Liao, et al., teach that "HMG-CoA reductase inhibitor such as simvastatin, pravastatin, fluvastatin, cerivastatin, atorvastatin are useful for the treatment of impotence" (Paper No. 01242005, page 6). However, Halkin (Ann. Pharmacother. 30:192, 1996) and Boyd (Ann. Pharmacother. 30:119, 1996) state that HMG-CoA reductase inhibitors actually cause impotence (copies of the references have been provided to the Examiner). Specifically, the authors describe case reports where patients treated with simvastatin, pravastatin, and lovastatin experienced impotence. Based on the disclosure of these references, one skilled in the art would not have been motivated to combine these components, an HMG-CoA reductase inhibitor and vardenafil, based on their "individually known common utility." That is, HMG-CoA reductase inhibitors appear to be a cause for impotence, not a treatment for impotence; and as such, there is no "common utility." Furthermore, the Examiner stated that one would have been motivated to combine these agents "to achieve expected additive benefit in treatment of impotence or even synergistic effect as taught by Liao et al." (Paper No. 01242005, page 7).

Obviously, since HMG-CoA reductase inhibitors cause impotence, then one would not expect an additive benefit or synergistic effect by combining an HMG-CoA reductase inhibitor and vardenafil.

In fact, the disclosure by Liao, et al., actually represents an "obvious-to-try" situation. That is, this general disclosure does not contain a sufficient teaching of how to obtain the claimed invention. The prior art provides no indication of which parameters are critical (e.g., dosage) or no direction as to which of the many possible choices is likely to be successful. Liao, et al., disclose numerous disease indications, numerous HMG-CoA reductase inhibitors, and numerous second agents, but one skilled in the art would have no idea which disease indication and which combination of HMG-CoA reductase inhibitors and second agents would actually be successful. Moreover, there is no guidance as to effective dosages, treatment schedules, etc.

"Obvious-to-try" is not the standard under 35 U.S.C. § 103 (In re O'Farrell, 853 F.2d 894). A claimed invention is obvious-to-try if the prior art gives "only general guidance as to the particular form of the claimed invention or how to achieve it" (In re O'Farrell, 853 F.2d 894, 903). Furthermore, "whether a particular combination might be obvious-to-try is not a legitimate test of patentability" (In re Fine, 837 F.2d 1071, 1075). As discussed above, the disclosure of Liao, et al., provides little guidance as to which combination would likely to be successful. Thus, the combination of the claimed invention may be obvious-to-try based on Liao, et al., but certainly not obvious.

As discussed in the response mailed March 5, 2004, the deficiencies of Liao, et al., are not remedied by Niewohner, et al. Niewohner, et al., discloses 2-[2-ethoxy-5-(4-ethyl-piperazine-1-sulfonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f]-[1,2,4]-triazin-4-one; however, Niewohner, et al., does not teach or suggest the combination of 2-[2-ethoxy-5-(4-ethyl-piperazine-1-sulfonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f]-[1,2,4]-triazin-4-one and HMG-CoA reductase inhibitors. Furthermore, based on the disclosure of Niewohner, et al., one skilled in the art would not have been motivated to combine 2-[2-ethoxy-5-(4-ethyl-piperazine-1-sulfonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f]-[1,2,4]-triazin-4-one and HMG-CoA reductase inhibitors to treat sexual dysfunction.

Likewise, neither Doherty, et al., nor R&D Drug News teach or suggest the combination of 2-[2-ethoxy-5-(4-ethyl-piperazine-1-sulfonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f]-[1,2,4]-triazin-4-one and HMG-CoA reductase inhibitors. Both the suggestion and the reasonable expectation of success are lacking.

It is therefore respectfully submitted that Liao, et al., either singly or in combination with Niewohner, et al., Doherty, et al., and R&D Drug Review, fail to teach or suggest the combinations or methods as presently claimed, and that the current invention is novel and nonobvious in view of the prior

art references. For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the present rejection.

CONCLUSION

For the foregoing reasons, Applicants submit that the claims are in condition for allowance and Applicants respectfully request reexamination of the present application, and reconsideration and withdrawal of the present rejections. Should there be any further matter requiring consideration, Examiner Kim is invited to contact the undersigned counsel.

If there are any further fees due in connection with the filing of the present reply, please charge the fees to undersigned's Deposit Account No. 13-3372. If a fee is required for an extension of time not accounted for, such an extension is requested and the fee should also be charged to undersigned's deposit account.

Respectfully submitted,

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HMG-CoA reductase inhibitor-induced impotence

TO THE EDITOR: 3-Hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors are used commonly for lowering total cholesterol and low-density lipoprotein (LDL) concentrations. Adverse effects attributed to these drugs are relatively uncommon and include gastrointestinal symptoms, myalgias, myopathy, headache, blurred vision, rash, and increased aminotransferase concentrations.[1] We report an association between lovastatin and pravastatin use and reversible impotence.

Case Report. A 57-year-old man with severe coronary artery disease receiving metoprolol, nifedipine, and aspirin began lovastatin therapy at a daily dose of 40 mg for hyperlipidemia type IIb. After 4 weeks of therapy the patient became impotent. Eight weeks later, he independently stopped taking lovastatin and his impotence resolved within 2 weeks. One year later, he was seen again in the clinic and was still taking metoprolol, nifedipine, and aspirin. Total cholesterol and LDL concentrations had been increased persistently, and treatment with pravastatin was initiated at a daily dosage of 20 mg. Following 3 weeks of treatment, impotence recurred. Pravastatin therapy was stopped and the patient regained normal sexual function within 2 weeks while continuing all other medications.

Discussion. The onset of impotence in relation to lovastatin administration, its disappearance after therapy had been discontinued, and its recurrence after rechallenge with pravastatin implicates this association as a possible causal class effect. We are unaware of a previous report associating these medications with sexual dysfunction, although this has been reported with other cholesterol-lowering agents.[2] In view of the recently reported induction of peripheral neuropathy shortly following administration of these medications,[3] neurologic dysfunction may contribute to impotence induced by HMG-CoA reductase inhibitors. Beta-adrenergic blocking agents are used commonly in conjunction with cholesterol-lowering drugs. Impotence induced by beta-blockers is cited commonly, although its true incidence is uncertain.[4,5] This adverse effect may be caused by an interaction between the two classes of drugs. In light of our observation, physicians treating patients taking such combined therapy should consider the cholesterol-lowering medication as well as beta-blockers as a possible cause of impotence.

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Gait ataxia during omeprazole therapy

TO THE EDITOR: Omeprazole is a proton-pump inhibitor widely used for the treatment of peptic ulcer, erosive reflux esophagitis, and the Zollinger-Ellison syndrome. The drug has been found to be well tolerated in clinical practice, with a low incidence of adverse effects. We report a case of gait ataxia probably induced by omeprazole, which was reversible after withdrawal of the drug.

Case Report. A 27-year-old woman reported a gait disturbance. She was well until 3 weeks earlier when she first noticed unsteadiness of stance and gait and a sensation of near-falling. Eventually, she experienced an episode of transient horizontal diplopia. The patient denied motor or sensory impairment, tremor, vertigo, or other symptoms of brainstem dysfunction. She had been taking omeprazole 60 mg/d for 4 months to alleviate heartburn associated with reflux esophagitis. Her family history was unremarkable.

On examination, her gait was wide-based and unsteady, without side-to-side deviations. She was neither uncoordinated nor dysarthric. Cranial nerves were intact. No sensory defect was elicited. Deep tendon reflexes were mildly asymmetric (3+ on the left and 2+ on the right). A posterior fossa lesion was suspected. Both cranial magnetic resonance imaging and multimodal evoked potentials were normal. Meanwhile, the patient had discontinued omeprazole and reported complete clinical recovery.

Discussion. Minor and serious adverse effects classified as possibly related to proton-pump therapy have been described in up to 3.5% of patients. These include headache, leukopenia, diarrhea, dizziness, and skin rash.[1,2] In an evaluation of toxic effects reported to pharmacovigilance centers in France, 26% of the reports involved neurologic or psychiatric effects, especially in patients with hepatic disease and/or advanced age.[3] Omeprazole is metabolized in the liver via the cytochrome P450 system and interactions with drugs metabolized by the same system, like benzodiazepines, are possible and may account for central nervous system toxicity in the elderly.[4] However, our patient was a young adult taking no other drugs and without clinical or laboratory evidence of hepatic disease. Ataxia has not been reported as an omeprazole-related adverse effect. Lack of family history, normal results on imaging and electrophysiologic examinations, and reversibility of signs and symptoms after withdrawal of the drug suggest omeprazole therapy as the cause of the gait disorder.

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Partition coefficient determination of antimuscarinic compounds

TO THE EDITOR: Muscarinic antagonists have proven useful in the treatment of various forms of rhinitis. The ability of atropine to block both hypersecretion and vasodilation induced by parasympathetic stimulation suggests that these actions are mediated through cholinergic muscarinic receptors.[1] Although effective in various forms of rhinitis, this action may be especially beneficial in cases of acute rhinorrhea. Because of their drying effect on nasal secretions, antimuscarinic agents are common constituents of a variety of oral proprietary cold/allergy products. However, despite their beneficial drying effects, anticholinergic therapy can be associated with a variety of adverse effects, including a spectrum

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Comment: HMG-CoA reductase inhibitor-induced impotence

TO THE EDITOR: I was interested by a recent report on the occurrence of impotence in association with the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors lovastatin and pravastatin.[1] The Adverse Drug Reactions Advisory Committee (ADRAC) has recently reported 28 cases of impotence in association with another HMG-CoA reductase inhibitor, simvastatin.[2]

Currently, ADRAC has received 42 reports of impotence in association with simvastatin. The men affected ranged in age from 43 to 72 years (median 57) and the onset occurred from 48 hours to 27 months (median ~6 wk) after the drug was started. Simvastatin was the only drug implicated in 35 of the reports, and in 4 patients, the problem recurred on rechallenge. Of the 29 reports in which recovery was mentioned, 14 patients had recovered after discontinuing the drug, whereas for the other 15, there had been no recovery at the time the report was submitted.

Impotence has been reported to ADRAC in association with simvastatin more often than any other drug. Lovastatin is not available in Australia and there are no reports of impotence in association with pravastatin, although this latter drug has achieved limited market penetration to date. There have also been reports to ADRAC of impotence in association with other lipid-lowering agents: 11 in association with clofibrate and 6 in association with gemfibrozil. As indicated by Halkin et al.,[1] impotence has also been associated with beta-blocker use, but ADRAC has received reports of the problem associated with many antihypertensive drugs. Use of lipid-lowering agents and any antihypertensive drug should be considered as a possible cause of impotence.

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Comment: delirium probably induced by clarithromycin in a patient receiving fluoxetine

TO THE EDITOR: In the case report entitled "Delirium Probably Induced by Clarithromycin in a Patient Receiving Fluoxetine,"[1] a man receiving long-term fluoxetine and nitrazepam therapy exhibited a change in personality when clarithromycin was given for a respiratory infection. After 72 hours the patient had developed bizarre behavior and was diagnosed with psychosis. Thirty-six hours after all three medications were stopped and erythromycin therapy was begun, the patient's mental state returned to normal. The psychiatric symptoms did not recur with further treatment with erythromycin or after restarting both fluoxetine and nitrazepam without antibiotics. The authors concluded that the patient's delirium was the result of fluoxetine intoxication caused by inhibition of cytochrome P450 (CYP) metabolism by clarithromycin. We would like to offer another possible explanation for the patient's change in mental status.

Both fluoxetine and its metabolite norfluoxetine are metabolized by CYP2D6.[2] Other enzymes that contribute to this metabolism are not known. Clarithromycin, on the other hand, inhibits the CYP3A enzymes by a unique mechanism in which clarithromycin and its metabolite form a complex with the enzymes.[3] Though not extensively studied, clarithromycin is probably similar to its analog erythromycin in that it is specific for the 3A family.[4] Thus, it seems highly unlikely that clarithromycin would produce substantial inhibition of fluoxetine metabolism given the differences in enzymes involved. Furthermore, at steady-state, fluoxetine has a half-life ($t_{1/2}$) of approximately 6 days.[5] Thus, even if one assumes that clarithromycin can increase fluoxetine concentrations through enzyme inhibition, the concentrations would have increased very slightly in the 24–72 hours during which the patient's psychiatric symptoms developed. They also would not have dissipated substantially in the 36 hours following discontinuation of the patient's medications.

Nitrazepam is reported to have a $t_{1/2}$ of 26 hours.[6] Though the cytochrome P450 enzyme involved in nitrazepam metabolism is not conclusively known, its metabolism might be inhibited by clarithromycin. However, with a $t_{1/2}$ of 26 hours, it seems unlikely that concentrations would have increased enough in 24–72 hours to cause delirium, nor decreased enough in 36 hours for the delirium to completely resolve in that time. The patient did not experience delirium or any central nervous system adverse effects other than drowsiness during a subsequent nitrazepam overdose. This lends further credence to the supposition that nitrazepam was not the cause of the patient's delirium.

Fluoxetine can inhibit CYP3A4, the enzyme responsible for clarithromycin and erythromycin metabolism.[7] This inhibition would also occur with the subsequently administered erythromycin, because even though fluoxetine was discontinued, the $t_{1/2}$ is such that fluoxetine would still be "on board" and CYP3A4, and thus erythromycin metabolism, would remain inhibited.

We believe that the observed change in mental status was the result of an idiosyncratic reaction to clarithromycin. This hypothesis would be in agreement with the rapid onset and resolution of delirium symptoms since clarithromycin has a $t_{1/2}$ of only 2.8–3.8 hours, and thus would be expected to rapidly disappear from the body.[7] When erythromycin was started, fluoxetine and nitrazepam would still have been within therapeutic concentrations due to their long $t_{1/2}$s, yet the mental status changes resolved. This lends further support to the hypothesis that the observed delirium may have been an idiosyncratic reaction to clarithromycin. Whether this patient's delirium was the result of elevated clarithromycin or nitrazepam concentrations or simply an idiosyncratic reaction to clarithromycin, it seems highly unlikely that the delirium was due to fluoxetine intoxication since a significant elevation in the concentrations of fluoxetine would not have occurred or dissipated during the period of time presented in this report. Unfortunately, without pre- and postclarithromycin concentrations of fluoxetine and nitrazepam or rechallenge with clarithromycin, the true cause of this patient's delirium will never be conclusively known. Thus, clinicians must be very careful when suggesting causation of an adverse event. We must look at all possible scenarios, eliminate those that are least probable, and base any hypotheses on scientific evidence rather than drawing conclusions just because a drug is known to produce adverse effects.

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Comments on articles previously published are submitted to the authors of those articles. When no reply is published, either the author chose not to respond or did not do so in a timely fashion.—ED.